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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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09/288,326 04/08/99 SACHS

G 17282

ALLERGAN INC
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HM12/0926

EXAMINER

CLEMENS, K

ART UNIT	PAPER NUMBER
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1644

DATE MAILED:

09/26/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.

09/288,326

Applicant(s)

SACHS ET AL.

Examiner

Karen Clemens

Art Unit

1644

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

- 1) ☒ Responsive to communication(s) filed on 24 July 2000.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-24 is/are pending in the application.
- 4a) Of the above claim(s) 9-12 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-8 and 13-24 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).
- a) ☐ All b) ☐ Some * c) ☐ None of the CERTIFIED copies of the priority documents have been:
1. ☐ received.
2. ☐ received in Application No. (Series Code / Serial Number) _____.
3. ☐ received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

- 14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

- 15) ☐ Notice of References Cited (PTO-892)
- 16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____
- 18) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 19) ☐ Notice of Informal Patent Application (PTO-152)
- 20) ☐ Other: _____

DETAILED ACTION

1. Applicant's amendment, received 7-24-00 (Paper No. 8), is acknowledged.
2. Claims 1-24 are pending.

Claims 9-12 stand withdrawn from further consideration by the examiner, 37 C.F.R. § 1.142(b) as being drawn to a nonelected invention.

Claims 1-8 and 13-24 are under examination.

3. Applicant's species election of SEQ ID NO:6 as the specific binding element is traversed based on the fact that the specific binding elements of SEQ ID NOs:2-6, from SEQ ID NO:2 to 6, are progressively smaller polypeptides each containing the common 9 amino acid sequence of SEQ ID NO:6. Applicant's argue that SEQ ID NO: 2-5 would fall within the "comprising" language of SEQ ID NO:6 and should therefore not be restricted into species.

Examiner notes Applicant's argument that the peptides also possess a common function, binding to the CCK A receptor. However, the peptides possess different structures and at least two have different functional properties, as noted by Kreis et al (*Neuroscience Letters* 230(2):89-92). Consequently a search of one peptide may be overlapping but is not necessarily co-extensive with a search of the other. The restriction requirement is therefore still deemed proper and is made Final.

4. Claims 1-8 and 13-24 stand rejected.
5. Applicant's arguments, filed 7/24/00 (Paper No.8), have been fully considered but are not found convincing for the reasons of record set forth in Paper No. 7.
6. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

"A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made."

Claims 1-8 and 13-24 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Foster et al. (WO 9633273, 1996) in view of Gaisano et al. (*J. Biol. Chem.* 269(25):17062-17066, 1994) and Scheele et al. (*Gastroenterology* 92(2):345-353, 1987) and further in view of Dangl et al. (*EMBO J.* 7(7):1989-94, 1988), all of record for the reason set forth in Paper No. 7.

A. Applicant's argue that Foster et al. disclose the use of a neural cell-specific chimeric therapeutic polypeptide in which the specificity of the C-terminal region of a clostridial neurotoxin is altered to change specificity from one neural cell type to another. Applicant's argue that the function of neural cells, particularly with regard to the mechanisms and microenvironment of exocytosis, would be similar between neural cells but would not suggest the use of such a chimeric therapeutic polypeptide in other cell types, notably pancreatic cells.

Applicant's further argue that Gaisano et al. use the tetanus toxin light chain to cleave a subpopulation of the VAMP-2 protein found in pancreatic acinar cell zymogen granule membrane fractions *in vitro* by first permeabilizing the acinar cells with streptolysin O. Applicant's argue that Gaisano et al. mention two other studies that failed to find toxin-sensitive isoforms of the VAMP proteins in pancreatic acinar cells and therefore teach away from the claimed invention.

Finally, Applicant's argue that Scheele et al. only teach the impact of the secretagogues caerulein and carbamylcholine on zymogen granule exocytosis in pancreatic acinar cells which would only suggest a therapeutic approach involving competitors of these secretagogues to block zymogen granule exocytosis not the claimed composition.

B. However, the Examiner notes that Foster et al. teach the claimed composition, absent the immunoglobulin hinge region linker (Dangl et al.) comprising a binding element to a *neuronal cell surface marker* (C-terminal half of the clostridial neurotoxin heavy chain), a translocation element (N-terminal half of the clostridial neurotoxin heavy chain), and a therapeutic element (clostridial neurotoxin light chain) capable of cleaving one of the SNARE proteins, synaptobrevin, syntaxin or SNAP-25 which will inhibit vesicle exocytosis and secretion, and a spacer moiety separating the binding element and the translocation element. Foster et al. do not teach targeting a receptor on a pancreatic cell. However, Foster et al. replaced the binding element (or targeting moiety) of the composition with a binding element that targets a different cell type, albeit still a neuronal cell type. Foster et al. note that the binding element (targeting moiety) provides specificity for the neuron and can comprise one of many cell binding molecules such as antibodies, lectins and ligands to the receptors for hormones, cytokines, growth factors or neuropeptides which binds to a binding site which undergoes retrograde transport (see page 13, lines 9-17).

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Further, the Examiner notes that Gaisano et al. discuss that recent insights into the molecular mechanisms of regulated exocytosis in neuronal cells have demonstrated the fundamental components of membrane fusion machinery and that pancreatic acinar cells provide a valuable model to study exocytotic mechanisms in non-excitabile cells (see page 17062, column 1). Gaisano et al. further demonstrated that the tetanus toxin light chain, once gaining access to the inside of the cell by permeabilization, was able to block calcium stimulated exocytosis in pancreatic acinar cells supporting the hypothesis that molecular mechanisms regulating exocytosis from neuronal and neuroendocrine cells is also utilized by the exocrine (pancreatic) cells (see page 17062 column 2 and abstract). It was well known in the art at the time of the invention that the light chains of the Clostridial neurotoxins (see Niemann et al., 1449 Ref. AR) from *Clostridium tetani* and *Clostridium botulinum*, of which there are several types, cleave one or more members of the docking proteins, or the SNARES VAMP (synaptobrevin), syntaxin or SNAP-25, thereby inhibiting vesicle docking and exocytosis.

Further, the Examiner notes that Scheele et al. teach that excessive pancreatic zymogen granule exocytosis and enzyme release, regardless of the method of induction, result in serious pathologic sequelae such as acute pancreatitis with pancreatic edema, inflammation and necrosis. Furthermore, Pohl et al. note that CCK-8 binds to CCK-A receptors on pancreatic acinar cells with high affinity, which would target the composition specifically to pancreatic cells (see Pohl et al., page 18180, introduction in particular; Form 1449).

Therefore, it would be been obvious to one having ordinary skill in the art at the time the invention was made to design a composition consisting of a binding element, a translocation element, a therapeutic element and a spacer moiety as taught by Foster et al. which inhibits enzyme secretion from pancreatic acinar cells as taught by Gaisano et al. using the secretagogue, cholecystokinin (CCK of which the bioactive form is CCK 8) as taught by Scheele et al. which binds to CCK-A pancreatic receptors as taught by Pohl et al. One having ordinary skill in the art at the time the invention was made would have been motivated to use this composition to inhibit enzyme secretion from the pancreas by blocking enzyme exocytosis which is associated with serious pathologic sequelae such as acute pancreatitis as taught by Scheele.

7. No claim is allowed.

8. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

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A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Clemens whose telephone number is (703) 308-8365. The examiner can normally be reached Monday through Friday from 8:00 am to 5:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Karen Clemens, Ph.D.
Patent Examiner
Technology Center 1600
September 25, 2000

Patrick J. Nolan
PATRICK J. NOLAN, PH.D.
PRIMARY EXAMINER
9/25/00